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(54) Title: A FILM FOR TOPICAL USE IN THE TREATMENT OF WOUNDS

(57) Abstract

A film for topical use in the treatment of wounds comprising hyaluronic acid or salts thereof and hydrocolloid.

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A FILM FOR TOPICAL USE IN THE TREATMENT OF WOUNDS

The present invention relates to films for topical use in the treatment of wounds, and in particular to films comprising hyaluronic acid or salts thereof alone or in combination with a hydrocolloid, and a process for making films comprising hyaluronic acid or salts thereof alone or in combination with a hydrocolloid.

Hyaluronic acid is an acid complex carbohydrate functioning mainly as a binding and protective component in connective tissue. It is known that administration of exogenous hyaluronic acid determines an antiphlogistic and stimulating effect on the granulation tissue, which accelerates cicatrization and re-epithelialization of lesions.

Pharmaceutical compositions are known from European Patent Application No. 0 480 198 which contain the sodium salt of hyaluronic acid and antiseptic substances for topical use. These compositions are however in the form of emulsions or hydrogels. When used in the treatment of wounds these product forms can suffer from the disadvantage that they add liquid to the wound site which adds to the problem of management of wound exudate. In addition these product forms make it difficult to apply a known and uniform dose to the wound.

From Japanese Patent Application No. 268765 to Kiburn Foods Inc it is known to make sheets from hyaluronic acid salt fibrous crystals for use in the treatment of skin lesions. These fibrous crystal sheets suffer from the disadvantage that they are fairly brittle and do not conform readily to the wound site. In addition, being white and opaque, they do not allow visualisation of the wound without removal. An additional disadvantage which is particularly marked for the intended use is that in the manufacture of the crystals flammable, toxic organic solvents are used which may be left as traces in the dressing and potentially damage the wound.

We have now found that these problems are mitigated by the present invention which accordingly provides a film for topical use in the treatment of wounds comprising hyaluronic acid and hydrocolloid. The advantages of this film are that because the film is dry, exudate is readily absorbed by both the hyaluronic acid and the hydrocolloid and dosing is uniform and predictable. We also believe that the topical film of the invention contributes to haemostasis.

A further aspect of the invention provides a clear and continuous film for topical use in the treatment of wounds comprising hyaluronic acid. The use of a clear film gives the advantage of wound visualisation without removal of the dressing. The clear film assists in wound healing and haemostasis.

A further aspect of the invention provides a process for making a film comprising hyaluronic acid comprising the steps of:

(i) mixing the hyaluronic acid or the hyaluronic acid and hydrocolloid in water or a suitable solvent and,

(ii) casting said mixture onto a substrate to form a film.

The process according to the invention has the advantage of simplicity and aids the easy and controlled addition of other components. As the hyaluronic acid is water soluble potentially toxic organic solvents need not be used. Suitable solvents for use in place of or in addition to water are propylene glycol and glycerol.

Hyaluronic acid as used in the present invention is found as a naturally occuring substance in the intracellular matrix of connective tissue. Preferably it is used in compositions of the present invention in the form of its acid salt, most preferably the sodium salt. This ensures water solubility to the hyaluronic acid and gives instantaneous dosage to the wound site. Commercially available hyaluronic acid or salts thereof has molecular weights in the range of from 50,000 to 2,000,000. We have found that the molecular weight of the hyaluronic acid used influences the characteristics of the film. Thus hyaluronic acids of different molecular weight can be blended to create particularly flexible films or particularly strong films. The salts can be prepared

commercially in a bacterial fermentation process or from animal tissues using appropriate extraction techniques. Prokaryotic hyaluronic acid is less expensive than the tissue extracted version, has higher purity and is available in larger quantities. The films of the present invention preferably comprise up to 100% hyaluronic acid, more preferably from 0.1% to 90% of hyaluronic acid when the film further comprises hydrocolloid.

Suitable hydrocolloid materials for use in the present invention include sodium, calcium (or other alkali metal or alkaline earth metal salts thereof) carboxymethylcellulose sodium carboxymethyl cellulose being preferred, pectin, gelatin, guar gum, locust bean gum, collagen polyvinylalcohol, hydroxyethyl cellulose, polyvinyl pyrollidone, alginates and salts thereof, chitin, aloe vera, hydroxypropylmethylcellulose and gum karaya. The films of the present invention preferably comprise from 10% to 90% by weight of hydrocolloid.

The films of the invention may also comprise various optional ingredients such as antibacterial agents and pharmaceutical agents and/or excipients such as preservatives, humectants and plasticiers. Particularly preferred optional ingredients include silver sulphadiazine, polyvinylpyrrolidone iodine, chlorhexidine and metronidazole.

The following are representative examples of dressings

within the scope of the invention.

Example 1

A hyaluronic acid film was prepared by mixing prokaryotic sodium hyaluronate of molecular weight 1,570,000 (Batch No.5021) ex Pronova Biopolymers of Box 8, Alton, Hampshire, GU3 4Y2, United Kingdom in water using an overhead propeller to form a 2% by weight solution. The solution was coated onto Melinex S Film, a polyethylene terephthalate ex ICI Films, at a coating thickness of 2mm and oven dried overnight. The percentage of sodium hyaluronate in the final film was 100%.

Example 2

The following example shows the effect of hyaluronic acid containing films on skin lesions. In a porcine wound model study six wounds (0.5 cm in diameter and extending down to the level of the muscle fascia) were created on each of the porcine models in the study. A gauze dressing was applied to the freshly created wounds on day 0 for a period of 24 hours. The following treatments were applied to the wounds from day 1 post-operatively.

Treatment A	A film prepared by the method of Example 1 under V5 dressings.
Treatment B	Control

Dressings were changed on days 2,4,7,9 and 11. Evaluation of the healing of the wounds was undertaken by measurement of the contraction rate, laser Doppler evaluation of blood

flow and histological evaluation of biopsies including various stainings for identification and analysis.

The results of the measurements of contraction rates of the wounds showed a significant difference between the treatment and control.

Evaluation of the angiogenic response in the wounds showed that on day 4 there was no significant difference in perfusion levels between the treatments. However on day 7 the results showed that the mean perfusion levels in the Treatment A wounds were higher than the control.

The histological data showed that all the wounds followed a normal progression of wound healing. The Treatment A wounds showed more advanced fibroplasia with development of granulation tissue.

Example 3

Example 1 was repeated by preparing a 2.00% by weight solution of hyaluronic acid extracted from tissue, in this case rooster comb (Pentapharm, Basel, Switzerland) which was then cast onto Melinex S Film in a 2mm layer and dried overnight.

Example 4

Example 1 was repeated by preparing a 2.00% by weight solution of hyaluronic acid extracted from human umbilical

cord tissue (Sigma Chemical Co., Poole, Dorset, UK) which was then cast onto Melinex S Film in a 2 mm layer and dried overnight.

Examples 5 to 14

Films according to the invention were made from separate aqueous solutions of the ingredients as shown in the following table made according to the method of Example 1. The solutions were coated onto Melinex S Film, a polyethylene terephthalate ex ICI Films, at a coating thickness of 2mm and oven dried overnight. The resulting films had a thickness of 0.5mm.

Examples 15 to 28

Films according to the invention were made from separate aqueous solutions of the ingredients as shown in the following table made according to the method of Example 1 except that the coating thickness and drying times were varied to give a final film thickness of 0.5mm. In making films comprising PVP it was found possible to add powdered PVP direct to a fully hydrated solution of hyaluronic acid. In those films which optionally comprise co-solvents such as propylene glycol or glycerol these components were added as liquids to fully hydrated solutions of the other components. The addition of polyethylene glycol where present was made as a solid or molten solution to fully hydrated solutions of the other components. The solutions were coated onto a substrate for example metal, glass,

acetate,polystyrene or polypropylene and dried to a final thickness of 0.5mm.

The films comprising a mixture of hyaluronic acid and a hydrocolloid were found to have the advantage of increased film strength over films containing hydrocolloid alone. This can be seen by comparing the results of Example 15 with those obtained from a film made of hydrocolloid alone - the film of Example 15 had a Max. Force of 15 N while that of a hydrocolloid alone has a Max. Force of 2.6 N. The addition of hydrocolloids to the films is beneficial because some hydrocolloids are believed to have useful wound healing properties in their own right for example aloe vera and chitin. The films comprising a mixture of PVP and hyaluronic acid were found to be particularly strong. The films comprising glycol, glycerol or polyethylene glycol as co-solvents were found to be very flexible. The maximum force to break 10mm x 50mm x 0.5mm samples of the film and their extension at breaking were measured using a Texture Analyser (ex Stable Micro Systems) at a velocity of $0.5mms^{-1}$. The time taken for one of the samples to dissolve completely in 50 ml of water was measured and noted as the dissolution time.

Examples 15 to 19

These films were prepared from 1 to 2% by weight solutions of hyaluronic acid, and hydrocolloid. Films were prepared from the individual solutions and mixtures of different solutions. The films produced were clear and dissolved

rapidly (1-2 minutes)

Example 20

This film was prepared from a 1% prokaryotic solution of hyaluronic acid with 0.1% polyethylene glycol. The film was clear and dissolved readily.

Example 21

This film was prepared from a 20% solution of low molecular weight prokaryotic hyaluronic acid and was clear with a yellow to flesh coloured tint.

Example 22

This film was prepared as example 21 except that the solution additionally contained 0.2% propylene glycol. The film was clear with a flesh coloured tint.

Examples 23 to 25

These films were prepared from a mixture of hyaluronic acids of different molecular weights. The films were yellow to clear.

Examples 26 and 27

These films were prepared from solutions of high molecular weight prokaryotic hyaluronic acid and poly-

vinylpyrollidone. The films were very strong with parameters beyond the measuring capabilities of the equipment.

Example 29

A film was prepared from a solution comprising 1% by weight of prokaryotic hyaluronic acid and 0.5% by weight of polyethylene glycol according to the method described above. The resulting film was clear and continuous.

The maximum force to break 10mm x 50mm x 0.5mm samples of the film and their extension at breaking were measured using a Texture Analyser (ex Stable Micro Systems) at a velocity of $0.5mms^{-1}$. The time taken for one of the samples to dissolve completely in 50 ml of water was measured and noted as the dissolution time.

Dissolution time: 10 minutes
Force to break: 8.8 N
Extension at break: 20mm

Solution Composition % by weight of	Example Number									
	5	6	7	8	9	10	11	12	13	14
Hyaluronic Acid (Sodium Salt) of molecular weight 1,570,000 ex Pronova Biopolymers	0.50	0.50		0.58	0.80		1.00	1.00		2.00
Hyaluronic Acid (Sodium Salt) of molecular weight 80,000 ex Pronova Biopolymers			2.00			4.00			2.00	
Carboxymethyl cellulose Sodium	1.00	1.50	1.75	1.17	4.00	1.60	1.00	5.00	2.00	2.00
Sodium Alginate	1.00	1.00	1.75	1.17	1.17	1.60	1.00	1.00	2.00	2.00
Pectin	0.50	0.50		0.58	0.58	0.80	0.50	0.50	1.00	2.00
Glycerol	0.45	0.53	0.90	0.53	0.53	1.20	0.26	1.125	1.15	1.20
Film composition % by weight of Hyaluronic Acid	14.5	24.8	31.25	14.4	11.2	25.0	26.6	11.6	24.5	21.7

Solution Composition % by weight of	Example Number													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Hyaluronic Acid (Sodium Salt) of molecular weight 1,570,000	1	1	1	1	1	1			1	1	1	1	0.5	1
Carboxymethyl cellulose Sodium				1										
Hyaluronic Acid (Sodium Salt) of molecular weight 80,000							20	20	5	20	25			
Sodium Alginate			2	1										
Aloe Vera	1													
Chitin		2												
Hydroxypropylmethyl Cellulose				2										
Polyvinylpyrrolidone					5							10	20	
Polyethylene glycol 600						0.1								
Propylene glycol								0.2						
Film composition % by weight of Hyaluronic Acid	50	25	33	25	17	91	100	98	100	100	100	9.1	2.44	100
Dissolution Time (min)	1	2	2	2	2	5	5	15	4	5	15	8	12	1
Max force (N)	12	10	1.5	1	11	9.8	29	29	4.3	11	24	*	*	12
Extension (mm)	8	7	8	7	8	10	15	15	20	10	20	*	*	8

* The maximum force and extension values for these films could not be measured due to limitations of the test equipment. These films were however particularly strong.

CLAIMS

1. A film for topical use in the treatment of wounds comprising hyaluronic acid or salts thereof and hydrocolloid.

2. A clear and continuous film for topical use in the treatment of wounds comprising hyaluronic acid or salts thereof.

3. A clear and continuous film as claimed in claim 2 which further comprises hydrocolloid.

4. A process for making a film comprising hyaluronic acid or salts thereof comprising the steps of:
   (i) mixing the hyaluronic acid and hydrocolloid in a suitable solvent and,
   (ii) casting said mixture onto a substrate to form a film.

5. A process for making a film comprising hyaluronic acid or salts thereof comprising the steps of:
   (i) mixing the hyaluronic acid in a suitable solvent and,
   (ii) casting said mixture onto a substrate to form a film.

6. A process a claimed in claim 4 or claim 5 wherein the solvent is water.

7. Use of a composition comprising hyaluronic acid or salts thereof and hydrocolloid in the preparation of

a medicament for use in the treatment of wounds.

8. Use as claimed in claim 7 wherein the wounds are chronic wounds.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/03079

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L15/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 9221 Derwent Publications Ltd., London, GB; Class A96, AN 92-171836 XP002019574 & JP,A,04 108 733 (KIBUN FOOD CHEMIFA) , 9 April 1992 see abstract ---	1-8
X	EP,A,0 200 574 (KATAKURA CHIKKARIN CO LTD ;KOKEN KK (JP)) 5 November 1986 see page 8, line 14 - line 24 see page 9, line 9 - line 18; example 5 ---	1-5
X	EP,A,0 459 378 (FIDIA SPA) 4 December 1991 see claims --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP,A,0 378 852 (MERCK PATENT GMBH) 25 July 1990 see the whole document	1-8
A	WO,A,93 11803 (M U R S T) 24 June 1993 see claims	1-8
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr nal Application No
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